

REMARKS/ARGUMENTS

Claims 1–38 are pending in the application, of which claim 38 has been previously withdrawn from consideration.

Responsibility for prosecution has been transferred to new counsel. Applicants respectfully request the rejections of the pending claims be reconsidered and withdrawn in light of the remarks that follow.

A. The Rejection of Claims 1-5, 8-10 and 29-32 under § 103(a) Is Addressed

Claims 1–5, 8–10 and 29–37 (of which claims 1, 3 and 29 are independent) were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,426,615 to *Mehta* in combination with U.S. Patent No. 5,744,366 to *Kricka et al.* This rejection is respectfully traversed. One of ordinary skill would not have had a motivation to combine the teachings of these two references. *Even if* taken together, the skilled practitioner would not have been led to make the presently claimed invention. The instant claims recite devices for sensing and characterizing particles by the Coulter principle where the particles are passed through a conduit having "**a cross-section area of less than about $1\text{ }\mu\text{m}^2$** " (e.g., Claims 1 and 3) or methods for sensing and characterizing particles by the Coulter principle that includes passing a liquid suspension of particles through a conduit that has "**a cross sectional area of less than about $1\text{ }\mu\text{m}^2$** " (e.g., Claim 29). However, as discussed below, *Mehta* explicitly teaches away from devices with a cross-sectional area of less than about $1\text{ }\mu\text{m}^2$. *Kricka* describes devices and methods for measuring cell motility by methods unrelated to the Coulter principle. As described below, one of ordinary skill in the art would not have combined the references, because *Mehta* and *Kricka* describe entirely unrelated devices and methods. Even if combined, the teachings of *Kricka* would not have motivated one of ordinary skill to modify the cross sectional area of the *Mehta* device, because *Mehta* teaches away from such a modification and *Kricka* is completely silent the topic of conduit aperture size and cross-sectional area in Coulter devices.

By way of brief background, the present invention relates to devices for sensing and characterizing particles by the Coulter principle. This principle allows the sizes of particles

to be determined by measuring changes in electrical conductivity as the particles pass through a fluid conduit. The particles in a solution that pass through the conduit displace some of the conducting solvent, thereby changing the electrical resistance of the conduit. By monitoring the changes in electrical current through the conduit as individual particles pass through, the sizes of the particles may be deduced. In conventional Coulter counters, the conduits in which particles are measured typically have conduit pore diameters between 15 and 200 μm , and conduit length-to-diameter ratios (L/D ratios) between 0.75 and 1.2. These conventional counters are able to resolve particle sizes down to about 0.6 μm . *See* Specification at paragraph [0007]. In contrast, the present invention provides Coulter devices with conduits that have cross-sectional areas and lengths that allow particles to be measured down to sizes of less than 100 nm (*i.e.*, less than 0.1 μm). *See, e.g.*, Specification at paragraph [0092].

The Office Action asserts that *Mehta* suggests making and using Coulter counters with a cross-section area of less than about 1 μm^2 . Office Action, paragraph 4. This assertion is based on a passage that discusses Coulter counters with "a sub-micrometer aperture." *Mehta*, Col. 1, lines 58–61. However, far from suggesting the utility of sub-micrometer apertures, *Mehta* in fact **teaches away** from making apertures this small because the measurement signal is obscured by noise:

For small particles, the electrical and acoustic noise compete with the small resistive pulse signal generated by the particles resulting in low S/N ratio. Therefore, the smallest particle measurable by the aperture impedance principle is typically 2% of the aperture diameter. With very small apertures, such as **a sub-micrometer aperture**, the lower limit is higher than 2% because **the noise floor rises substantially due to the increased resistance**. The noise goes as the square root of the aperture resistance and the aperture resistance is inversely proportional to the square of the aperture cross-sectional area. Therefore, **as the aperture becomes smaller, the resistance increases and so does the associated noise**. Additionally, for the instruments based on this aperture impedance or electrical sensing zone method, in the measurement of small particles, thermal aperture noise continues to exceed all other noise contributions by more than an order of magnitude. Further improvements in the circuitry cannot lead to better resolution.

Mehta, Col. 1, line 54 to Col. 2, line 4. In light of this teaching, Applicants respectfully submit the Office has failed to establish a *prima facie* case of obviousness.

The second reference, *Kricka*, describes a device for analyzing the motility of mobile cells, such as sperm cells. The Office characterizes *Kricka* as disclosing "a device for characterizing particles" (Office Action at paragraph 5). However, the *Kricka* device characterizes cells based on motility. The reference makes no mention of Coulter counters or the Coulter principle. The reference is completely silent the topic of conduit aperture size and cross-sectional area in such counters. The Office has not set forth any theory under which one of ordinary skill in the art would have combined the teachings of these references. Applicants respectfully submit it is clear there would not have been any such motivation. Again, Applicants respectfully submit the Office has failed for multiple reasons to establish a *prima facie* case of obviousness.

Still further, *even if* combined, the teachings of *Kricka* in combination with those of *Mehta* would not have resulted in the presently claimed invention. *Kricka* is completely silent on devices that sense and characterize particles by the Coulter principle, while *Mehta* teaches away from Coulter counters having the cross-sectional area recited in claims 1, 3 and 29. There would not have been a motivation to modify the *Mehta* device based *Kricka* to make the invention of claims 1, 3 and 29, the references do not satisfy the requisite criteria for establishing a case of *prima facie* obviousness with respect to the claims.

Accordingly, claims 1, 3 and 29 are allowable over the combination of *Mehta* and *Kricka*. For at least the same reason, claims 2, 4–10 and 30–37, which depend from claims 1 and 29, respectively, are allowable over the references as well. Withdrawal of the rejection of claims 1–5, 8–10, and 29–37 under § 103(a) over the combination of *Mehta* and *Kricka* is respectfully requested.

B. The Rejection of Independent Claims 11 and 22 and Dependent claims 12-21 and 23-28 under § 103(a) Is Addressed

The Office Action also includes a rejection of claims 11–28 over the combination of *Mehta* and *Kricka*. This rejection is also traversed because one of skill in the art would have

had no motivation to combine the references to make a Coulter device with a conduit formed at least in part by an elastomeric material. Independent claims 11 and 22 include a Coulter device and method, respectively, which use **"a conduit formed at least in part by an elastomeric material."** Elastomeric materials have relatively low dielectric constants, which decrease the parasitic capacitance in the conduit, and increase the achievable time resolution for particle measurements based on the Coulter principle. *See* Specification at paragraph [0036].

The Office Action acknowledges *Mehta* "fails to teach forming the conduit at least in part by an elastomeric material." *See* Office Action, Page 3, Item 10. To rectify this deficiency, the Office cites *Kricka* for its description of a conduit in a completely unrelated device that can be made of elastomeric material. As noted above, *Kricka* describes a device for measuring cell motility (*e.g.*, the movement strength of sperm cells) by having the cells propel themselves through a strait or crooked fluid channel. *See Kricka*, Col. 3, lines 48–54. The cells are observed in the channel with an optical microscope, and there is no suggestion that measurements based on the Coulter principle (or any kind of electrical property) are performed. *See, e.g., Kricka*, Col. 11, lines 31–36.

There is no suggestion in either reference that elastomeric materials could have been used in a conduit to improve the measurement properties of a Coulter device. Thus, one of skill in the art would have had no motivation to combine the references to make the device of claim 11 or practice the method of claim 22. For at least this reason, claims 11 and 22 are allowable over the combination of *Mehta* and *Kricka*. For at least the same reason, claims 12–21 and 23–28, which depend from claims 11 and 22, respectively, are allowable over the references as well. In addition, some of the dependent claims recite additional elements like having a conduit with "a cross-sectional area of between about $1\text{ }\mu\text{m}^2$ or less", which are also allowable over the combination of *Mehta* and *Kricka*. Accordingly, withdrawal of the rejection of claims 11–28 under § 103(a) over the combination of *Mehta* and *Kricka* is respectfully requested.


CONCLUSION

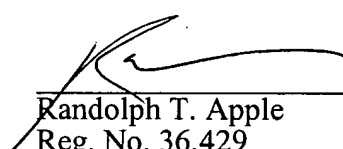
In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

Please charge Deposit Account No. 24-1430 the \$490 fee for a 3-month extension of time under 37 C.F.R. §1.136(a)(1), and \$170.00 fee for filing a Notice of Appeal under 37 C.F.R. §41.20(b)(1). No other fees are believed to be due with this Response, but should any be required, please charge the above-identified deposit account for any fee deficiency.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,


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C. The Rejection of Claims 6 and 7 under § 103(a) Is Addressed

Finally, the Office Action included a rejection of claims 6 and 7 under § 103(a) over *Mehta* and *Kricka*, and in further view of U.S. Patent No. 6,168,948 to *Anderson et al.* Claims 6 and 7 depend from claim 1, and as noted above, one of skill in the art has no motivation to make a Coulter device having a conduit with a cross-sectional area of less than about $1 \mu\text{m}^2$ based on *Mehta* and *Kricka*. *Anderson*, which describes a nucleic acid diagnostic and sequencing device, does not remedy the deficiencies of *Mehta* and *Kricka*. Accordingly, withdrawal of the rejection of claim 6 and 7 under § 103(a) over *Mehta*, *Kricka* and *Anderson* is respectfully requested.